



PTO/SB/08A (10-01)

Approved for use through 10/31/2002. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Institute for form 1449A/PTO

## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet

1

of

7

### Complete if Known

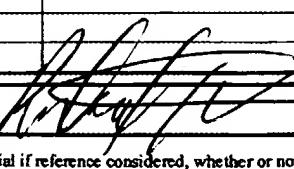
Application Number	09/830,502
Filing Date	October 29, 1999
First Named Inventor	Barany et al.
Art Unit	1652
Examiner Name	R. Hutson
Attorney Docket Number	19603/2615 (CRF D-2408)

### U.S. PATENT DOCUMENTS

Examiner Initials	Cite No. <sup>1</sup>	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YYYY		
RH	1	US-4,683,202	07/28/1987	Mullis	
	2	US-4,883,750	11/28/1989	Whiteley et al.	
	3	US-5,470,705	11/28/1985	Grossman et al.	
	4	US-6,576,453	06/10/2003	Barany et al.	
	5	US-6,054,564	04/25/2000	Barany et al.	
	6	US-5,494,810	02/27/1996	Barany et al.	
	7	US-5,496,699	03/05/1996	Sorenson	
	8	US-5,506,137	04/09/1996	Mathur et al.	
	9	US-5,516,663	05/14/1996	Backman et al.	
	10	US-5,728,526	03/17/1998	George, Jr. et al.	
	11	US-5,912,148	06/15/1999	Eggerding	
RH	12	US-6,312,892	11/06/2001	Barany et al.	
		US-			

### FOREIGN PATENT DOCUMENTS

Examiner Initials	Cite No. <sup>1</sup>	Foreign Patent Document		Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>4</sup>
		Country Code <sup>3</sup> Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)			
RH	13	WO 91/17239	11/14/1991	WIPO		
	14	WO 98/03673	01/29/1998	WIPO		
	15	WO 00/26381	05/11/2000	WIPO		
	16	WO 97/31256	08/28/1997	WIPO		
	17	WO 97/45559	12/04/1997	WIPO		
RH	18	WO 93/17126	09/02/1993	WIPO		

Examiner Signature		Date Considered	9/29/04
--------------------	---	-----------------	---------

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See Kinds Codes of USPTO Patent Documents at 222.uspto.gov or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**  
*(use as many sheets as necessary)*

Sheet

2

of

7

*Complete if Known*

Application Number	09/830,502
Filing Date	October 29, 1999
First Named Inventor	Barany et al.
Group Art Unit	1652
Examiner Name	R. Hutson
Attorney Docket Number	19603/2615 (CRF D-2408)

**OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS**

Examiner Initials <sup>1</sup>	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
RK	19	Kreiner, T., "Rapid Genetic Sequence Analysis Using a DNA Probe Array System," <i>American Laboratory</i> 39-43 (March 1996)	
	20	Kovach et al., "Mutation Detection by Highly Sensitive Methods Indicates That p53 Gene Mutations in Breast Cancer Can Have Important Prognostic Value," <i>Proc. Natl Acad. Sci. USA</i> 93:1093-96 (1996)	
	21	Lin et al., "Multiplex Genotype Determination at a Large Number of Gene Loci," <i>Proc. Natl. Acad. Sci. USA</i> 93:2582-87 (1996)	
	22	Tavormina et al., "Thanatophoric Dysplasia (Types I and II) Caused by Distinct Mutations in Fibroblast Growth Factor Receptor 3," <i>Nature Genetics</i> 9:321-328 (1995)	
	23	Barany et al., "Cloning, Overexpression and Nucleotide Sequence of a Thermostable DNA Ligase-Encoding Gene," <i>Gene</i> 109:1-11 (1991)	
	24	Sidransky et al., "Identification of <i>ras</i> Oncogene Mutations in the Stool of Patients With Curable Colorectal Tumors," <i>Science</i> 256:102-105 (1992)	
	25	Brennan et al., "Molecular Assessment of Histopathological Staging in Squamous-Cell Carcinoma of the Head and Neck," <i>The New England Journal of Medicine</i> 332(7):429-35 (1995)	
	26	Berthélémy et al., "Identification of K-ras Mutations in Pancreatic Juice in the Early Diagnosis of Pancreatic Cancer," <i>Annals of Internal Medicine</i> 123(3):188-91 (1995)	
	27	Hayashi et al., "Genetic Diagnosis Identifies Occult Lymph Node Metastases Undetectable by the Histopathological Method," <i>Cancer Research</i> 54:3853-56 (1994)	
RK	28	Tada et al., "Detection of <i>ras</i> Gene Mutations in Pancreatic Juice and Peripheral Blood of Patients with Pancreatic Adenocarcinoma," <i>Cancer Research</i> 53:2472-74 (1993)	

Examiner Signature	<i>R. Hutson</i>	Date Considered	9/29/04
--------------------	------------------	-----------------	---------

<sup>1</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>2</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.



Substitute for form 1449B/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**  
*(use as many sheets as necessary)*

Sheet

3

of

7

*Complete if Known*

Application Number	09/830,502
Filing Date	October 29, 1999
First Named Inventor	Barany et al.
Group Art Unit	1652
Examiner Name	R. Hutson
Attorney Docket Number	19603/2615 (CRF D-2408)

**OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS**

Examiner Initials <sup>1</sup>	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
RH	29	Tada et al., "Clinical Application of <i>ras</i> Gene Mutation for Diagnosis of Pancreatic Adenocarcinoma," <i>Gastroenterology</i> 100:233-38 (1991)	
	30	Mitsudomi et al., "Mutations of <i>ras</i> Genes Distinguish a Subset of Non-Small-Cell Lung Cancer Cell Lines From Small-Cell Lung Cancer Cell Lines," <i>Oncogene</i> 6:1353-62 (1991)	
	31	Day et al., "Detection of Steroid 21-Hydroxylase Alleles Using Gene-Specific PCR and a Multiplexed Ligation Detection Reaction," <i>Genomics</i> 29:152-62 (1995)	
	32	Frenkel et al., "Specific, Sensitive, and Rapid Assay for Human Immunodeficiency Virus Type 1 <i>pol</i> Mutations Associated With Resistance to Zidovudine and Didanosine," <i>J. Clin. Microbiol.</i> 33(2):342-47 (1995)	
	33	Abraaya et al., "Detection of Point Mutations With a Modified Ligase Chain Reaction (Gap-LCR)," <i>Nucleic Acids Research</i> 23(4):675-82 (1995)	
	34	Powell et al., "Molecular Diagnosis of Familial Adenomatous Polyposis," <i>The New England Journal of Medicine</i> 329(27):1982-87 (1993)	
	35	Jen et al., "Molecular Determinants of Dysplasia in Colorectal Lesions," <i>Cancer Research</i> 54:5523-26 (1994)	
	36	Redston et al., "Common Occurrence of APC and K- <i>ras</i> Gene Mutations in the Spectrum of Colitis-Associated Neoplasias," <i>Gastroenterology</i> 108:383-92 (1995)	
	37	Lu et al., "Quantitative Aspects of the Mutant Analysis by PCR and Restriction Enzyme Cleavage (MAPREC)," <i>PCR Methods and Applications</i> 3:176-80 (1993)	
RH	38	Kuppuswamy et al., "Single Nucleotide Primer Extension to Detect Genetic Diseases: Experimental Application to Hemophilia B (factor IX) and Cystic Fibrosis Genes," <i>Proc. Natl. Acad. Sci. USA</i> 88:1143-47 (1991)	

Examiner Signature		Date Considered	9/29/05
--------------------	--	-----------------	---------

<sup>1</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>2</sup> Applicant's unique citation designation number (optional). <sup>3</sup> Applicant is to place a check mark here if English language Translation is attached.



Institute for form 1449B/PTO

## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet

4

of

7

**Complete if Known**

Application Number	09/830,502
Filing Date	October 29, 1999
First Named Inventor	Barany et al.
Group Art Unit	1652
Examiner Name	R. Hutson
Attorney Docket Number	19603/2615 (CRF D-2408)

**OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS**

Examiner Initials	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
RK	39	Rust et al., "Mutagenically Separated PCR (MS-PCR): A Highly Specific One Step Procedure for Easy Mutation Detection," <i>Nucleic Acid Research</i> 21(16):3623-29 (1993)	
	40	Suzuki et al., "Detection of <i>ras</i> Gene Mutations in Human Lung Cancers by Single-Strand Conformation Polymorphism Analysis of Polymerase Chain Reaction Products," <i>Oncogene</i> 5:1037-43 (1990)	
	41	Balles et al., "Facilitated Isolation of Rare Recombinants by Ligase Chain Reaction: Selection for Intragenic Crossover Events in the <i>Drosophila optomotor-blind</i> Gene," <i>Mol. Gen. Genet.</i> 245:734-40 (1994)	
	42	Reynolds et al., "Analysis of Genetic Markers in Forensic DNA Samples Using the Polymerase Chain Reaction," <i>Anal. Chem.</i> 63:2-15 (1991)	
	43	Buyse et al., "Rapid DNA Typing of Class II HLA Antigens Using the Polymerase Chain Reaction and Reverse Dot Blot Hybridization," <i>Tissue Antigens</i> 41:1-14 (1993)	
	44	Gyllensten et al., "PCR-Based HLA Class II Typing," <i>PCR Meth. Appl.</i> 1:91-98 (1991)	
	45	Chamberlain et al., "Deletion Screening of the Duchenne Muscular Dystrophy Locus Via Multiplex DNA Amplification," <i>Nucleic Acids Res.</i> 16:11141-56 (1988)	
	46	Tsui, L. C., "Mutations and Sequence Variations Detected in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene: A Report From the Cystic Fibrosis Genetic Analysis Consortium," <i>Human Mutat.</i> 1:197-203 (1992)	
	47	Hollstein et al., "p53 Mutations in Human Cancers," <i>Science</i> 253:49-53 (1991)	
RK	48	Saiki et al., "Enzymatic Amplification of $\beta$ -Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia," <i>Science</i> 230:1350-1354 (1985)	

Examiner Signature	<i>R. Hutson</i>	Date Considered	9/29/04
--------------------	------------------	-----------------	---------

<sup>1</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>2</sup> Applicant's unique citation designation number (optional). <sup>3</sup> Applicant is to place a check mark here if English language Translation is attached.



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449B/PTO				<i>Complete if Known</i>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> <i>(use as many sheets as necessary)</i>				Application Number	09/830,502
Sheet	5	of	7	Filing Date	October 29, 1999
				First Named Inventor	Barany et al.
				Group Art Unit	1652
				Examiner Name	R. Hutson
				Attorney Docket Number	19603/2615 (CRF D-2408)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS				
Examiner Initials <sup>1</sup>	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T <sup>2</sup>
RH	49	Wu et al., "The Ligation Amplification Reaction (LAR) -- Amplification of Specific DNA Sequences Using Sequential Rounds of Template-Dependent Ligation," <i>Genomics</i> 4:560-69 (1989)		
	50	Landegren et al., "A Ligase-Mediated Gene Detection Technique," <i>Science</i> 241:1077-80 (1988)		
	51	Winn-Deen, et al., "Sensitive Fluorescence Method for Detecting DNA Ligation Amplification Products," <i>Clinical Chemistry</i> 37(9):1522-23 (1991)		
	52	Barany, F., "Genetic Disease Detection and DNA Amplification Using Cloned Thermostable Ligase," <i>Proc. Nat'l Acad. Sci. USA</i> 88:189-93 (1991)		
	53	Grossman et al., "High-Density Multiplex Detection of Nucleic Acid Sequences: Oligonucleotide Ligation Assay and Sequence-Coded Separation," <i>Nucl. Acids Res.</i> 22(21):4527-34 (1994)		
	54	Jou et al., "Deletion Detection in the Dystrophin Gene by Multiplex Gap Ligase Chain Reaction and Immunochromatographic Strip Technology," <i>Human Mutation</i> 5:86-93 (1995)		
	55	Gibbs et al., "Detection of Single DNA Base Differences by Competitive Oligonucleotide Priming," <i>Nucleic Acids Res.</i> 17:2437-48 (1989)		
	56	Chehab et al., "Detection of Specific DNA Sequences by Fluorescence Amplification: A Color Complementation Assay," <i>Proc. Natl. Acad. Sci. USA</i> 86:9178-82 (1989)		
	57	Livak et al., "Detection of Single Base Differences Using Biotinylated Nucleotides With Very Long Linker Arms," <i>Nucleic Acids Res.</i> 20(18):4831-37 (1992)		
RH	58	Nickerson et al., "Automated DNA Diagnostics Using an ELISA-Based Oligonucleotide Ligation Assay," <i>Proc. Natl. Acad. Sci. USA</i> 87:8923-27 (1990)		

Examiner Signature		Date Considered	9/29/04
--------------------	--	-----------------	---------

<sup>1</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>2</sup> Applicant's unique citation designation number (optional). <sup>3</sup> Applicant is to place a check mark here if English language Translation is attached.



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Institute for form 1449B/PTO				<i>Complete if Known</i>	
				Application Number	09/830,502
				Filing Date	October 29, 1999
				First Named Inventor	Barany et al.
				Group Art Unit	1652
				Examiner Name	R. Hutson
Sheet	6	of	7	Attorney Docket Number	19603/2615 (CRF D-2408)

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS				
Examiner Initials <sup>1</sup>	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T <sup>2</sup>
RK	59	Dong et al., "Mutational Studies of Human DNA Polymerase $\alpha$ ," <i>J. Biol. Chem.</i> 268(32):24175-24182 (1993)		
	60	Copeland et al., "Fidelity Studies of the Human DNA Polymerase $\alpha$ ," <i>J. Biol. Chem.</i> 268(15):11041-11049 (1993)		
	61	Reha-Krantz et al., "Motif A of Bacteriophage T4 DNA Polymerase: Role in Primer Extension and DNA Replication Fidelity," <i>J. Biol. Chem.</i> 269(8):5635-5643 (1994)		
	62	Eggerding, F., "A One-Step Coupled Amplification and Oligonucleotide Ligation Procedure for Multiplex Genetic Typing," <i>PCR Methods and Applications</i> 4:337-345 (1995)		
	63	Friedhoff et al., "Quantitative Polymerase Chain Reaction with Oligodeoxynucleotide Ligation Assay/Enzyme-Linked Immunosorbent Assay Detection," <i>Anal. Biochem.</i> 215:9-16 (1993)		
	64	Wallace et al., "Ligase Chain Reaction for the Detection of Specific DNA Sequences and Point Mutations," in Pfeifer, ed., <i>Technologies for Detection of DNA Damage and Mutations</i> at 307-322, Plenum Press, New York, NY (1996)		
	65	Reyes et al., "Ligase Chain Reaction Assay for Human Mutations: The Sickle Cell by LCR Assay," <i>Clinical Chemistry</i> 43(1):40-44 (1997)		
	66	Jónsson et al., "Sequence of the DNA Ligase-Encoding Gene from <i>Thermus scotoductus</i> and Conserved Motifs in DNA Ligases," <i>Gene</i> 151:177-180 (1994)		
	67	Luo et al., "Improving the Fidelity of <i>Thermus thermophilus</i> DNA Ligase," <i>Nucleic Acids Res.</i> 24:3071-3078 (1996)		
	68	Luo et al., "Identification of Essential Residues in <i>Thermus thermophilus</i> DNA Ligase," <i>Nucleic Acids Res.</i> 24:3079-3085 (1996)		
	69	Tong et al., "Biochemical Properties of a High Fidelity DNA Ligase from <i>Thermus</i> Species AK16D," <i>Nucleic Acids Research</i> 27:788-794 (1999)		
	70	Zirvi et al., "Ligase-Based Detection of Mononucleotide Repeat Sequences," <i>Nucleic Acids Research</i> 27(24):e40i-e40viii (1999)		
RK	71	Ngo et al., "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox," in <i>The Protein Folding Problem and Tertiary Structure Prediction</i> , Merz et al., Eds., Boston, MA: Birkhauser, Chapter 14, pp. 491-495 (1994)		

Examiner Signature		Date Considered	9/19/04
--------------------	--	-----------------	---------

<sup>1</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

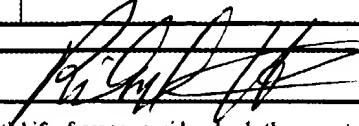
<sup>2</sup> Applicant's unique citation designation number (optional). <sup>3</sup> Applicant is to place a check mark here if English language Translation is attached.



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Institute for form 1449B/PTO				<i>Complete if Known</i>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> <i>(use as many sheets as necessary)</i>				Application Number	09/830,502
Sheet	7	of	7	Filing Date	October 29, 1999
				First Named Inventor	Barany et al.
				Group Art Unit	1652
				Examiner Name	R. Hutson
				Attorney Docket Number	19603/2615 (CRF D-2408)

OTHER PRIOR ART - NON PATENT LITERATURE DOCUMENTS				
Examiner Initials <sup>1</sup>	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.		T <sup>2</sup>
R K	72	Takahashi et al., "Purification of HB8 DNA Ligase by Red Sepharose Chromatography," <i>Agric. Biol. Chem.</i> 50(5):1333-1334 (1986)		
	73	Takahashi, M., et al., "Thermophilic DNA Ligase Purification and Properties of the Enzyme from <i>Thermus Thermophilus</i> HB8," <i>Biol. Chem.</i> 259(16):10041-10047 (1984)		
	74	Takahashi, M., et al., "Thermophilic HB8 DNA Ligase: Effects of Polyethylene Glycols and Polyamines on Blunt-End Ligation of DNA, <i>J. Biochem.</i> , 100:123-31 (1986)		
	75	Belgrader et al., "A Multiplex PCR-Ligase Detection Reaction Assay for Human Identity Testing," <i>Genome Science &amp; Tech.</i> 1:77-87 (1996)		
R K	76	Newton, "The Production of PCR Products with 5' Single-Stranded Tails Using Primers That Incorporate Novel Phosphoramidite Intermediates," <i>Nucleic Acids Research</i> 21(5): 1155-1162 (1993)		

Examiner Signature		Date Considered	11/29/04
--------------------	---	-----------------	----------

<sup>1</sup> EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>2</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached